UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,310	03/22/2001	Gavin C. Hirst	BBI-6072CP	4602

959 7590 05/30/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
HABTE, KAHSAY

ART UNIT	PAPER NUMBER
1624	11

DATE MAILED: 05/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/815,310	Applicant(s) HIRST ET AL.	
	Examiner Kahsay Habte, Ph. D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicants elected a single disclosed species (Example 207) in Paper No. 10 on 5/19/03. Since there is no prior art on the single species, the examiner has extended the search to the entire genius.

Abstract

2. Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

Applicants have to specify the utilities of the compounds or composition. Applicants also have to define the variable G.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 120 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for many of the diseases listed in claim 120, does not reasonably provide enablement for an ocular condition, cancer, chronic inflammation, cardiovascular condition and stroke. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to understand the invention commensurate in scope with these claims. There has been recited in claim 120, a method of treating an ocular condition, cancer, chronic inflammation, cardiovascular condition, and stroke, but the specification does not teach how to treat said diseases.

There has been recited in claim 120 a method of treating ocular condition (all pathological abnormalities of the eye) in general, but the specification is not enabled for such a scope. This means that the compound will treat diseases of the eye generally. There are scores of such diseases, arising from all kinds of sources, such as trauma, pregnancy, leukemia, excess light (photoretinopathy), rubella, hypertension arising from nephrosclerosis, diabetes, exudates of the eye, increased blood viscosity arising from dysproteinemia, CMV infections, neovascularization, side effect of other drugs (toxic retinopathy), excess oxygen arising from treatment of premature birth, a sudden rise in venous pressure, and other causes as well. Further, these retinopathies take many and quite varied forms, including degeneration of the choroid, hemorrhages, microaneurysms, edema of the retina, occlusion of the central retinal vein, retinal ischemia, angiospasms of retinal arterioles, various glaucomas such as primary open-

angle glaucoma, a neurodegenerative disorder, dilation of retinal veins, night blindness, papilledema, various forms of macular degeneration, retinal detachment, retrolental fibroplasia, and many other problems.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is aninflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with intravenous antibiotics.

The vast majority of these are not treatable by any pharmaceutical means. It would be contrary to medical understanding for any compound to be able to treat generally

problems, which are so different in both origin and effect. Such a thing is beyond the reach of modern medicine.

The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.
When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have

stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.
Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Cardiovascular disorders embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris; the thrombotic symptoms of diabetes,

atherosclerosis and hyperlipoproteinaemias; ischaemic heart disease including congestive heart failure and myocardial infarction; stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCA); elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol; arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. No one compound --- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such

as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well.

Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining a neuroprotective treatment of stroke was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there is cited Chalmers (TiPS Vol 17, pages 166-172 April 1996), which states flatly on page 170 that, "At present, there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." Lyrer (Schweiz. Med. Wochenschr., Vol 124, #45, 2005-2012 1994)

states in the summary, "Up to the present, treatment strategies for acute cerebral ischemia have not shown scientifically proven efficacy. It notes that trials on the use of cytoprotective agents "are ongoing or are planned", clear evidence of the research that remains to be done to determine how to treat stroke. For example, Pentoxifylline has been one of the most intensely studied, with dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Yet, as Frampton (Drugs and Aging 7(6) 480-503 1995) notes, it is still unclear whether this drug can be made to work against stroke. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. Applicants' compounds have been subjected to far less study.

4. Claim 115 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There has been recited a method of affecting hyperproliferative disorders, but the specification does not teach the method of affecting of the said disorder.

A proliferative disorder is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic Syndromes such as Refractory anemias, certain types of abnormal wound healings, different types of abnormal angiogenisis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, and rheumatoid arthritis. There is no such thing that an agent which is effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because the term "prodrugs" is indefinite. Determining whether a given derivative definitely is or is not a prodrug involves more than routine experimentation. If the derivative is active, open-ended experimentation may be involved to determine for sure whether the compound is a prodrug or whether it is active in its own right. .

b. In claim 1 (page 926, line 12) or elsewhere in the claims, the phrase "Z^{110}..an optionally substituted (C_1-C_6) which.." is not clear. What is it? Is it (C_1-C_6) alkyl? Or something else? The same is true for the phrase "Z^{105}.. covalent bond or (C_1-C_6) which.." and "Z^{200}.. substituted or unsubstituted (C_1-C_6) which.." etc.

c. In claim 1, the phrase "an optionally substituted (C_1-C_6)" is incorrect. It should read as "an optionally substituted (C_1-C_6)alkylene", since Z^{111} is divalent.

d. In claim 1 (page 927, line 19) or elsewhere in the claims, "amido" is indefinite. There is no way of knowing whether applicants intend just carboxylic acid amides, or whether sulfonic, phosphonic, etc. amides are intended. But even if carboxylic acid amido is intended, the term is undefined. Such a molecule generically has the formula RC(O)NR'R". One of the R choices will be used to attach, depending on whether the amido is C- or N-bound. Which end is intended for attachment? What is the nature of the other two R groups? Can the two of them together form a ring, and if so, of what type?

e. In claim 1 (page 930, line 11), the term "comprising" is open-ended language. It is recommended that applicant use "consisting of".

f. In claim 1 (page 930, line 22) or elsewhere in the claims, the term "azacycloalkyl" is indefinite. What are covered and what are not? Is there only one nitrogen in the ring and the rest carbon atoms? Are there more than one nitrogen in the ring and the rest carbon atoms? Can there be any heteroatoms present in addition to the nitrogen?

g. In claim 1, the phrase "biologically active metabolites" is not clear. How can one prove that a given compound is not an "active metabolite"? It is easy to prove that a compound is biologically active metabolite, but it is not easy to prove the negative.

The public has to know how to exclude biologically non-active compounds. Even if not found in blood or urine, it might have existed briefly as a metabolite.

h. In claim 113, the phrase "one or more protein kinase" is indefinite. There are at least 400 enzymes identified as protein kinase. Do applicants intend to claim all? Is a protein kinase AKT_h included? AKT2_h? PDK1? PK428_h?

i. Claim 126 is rejected because it fails to further limit claim 116. The phrase "an amount effective to promote angiogenesis or vasculogenesis" fails to further limit the phrase "method of affecting angiogenesis", because claim 116 would be understood as using that same amount.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mukund J. Shah
Supervisory Patent Examiner
Art Unit 1624

KH
May 28, 2003